REMARKS / ARGUMENTS

Upon entry of the present amendments, claims 35 and 39 are currently under consideration in the application. Claims 1-29 and 31-34 are withdrawn from consideration. Claim 30, and 36-38 are cancelled without prejudice. Support for amended claim 35 appears at least in original claim 1 and claim 3 as well as at page 4, lines 21-30 through page 6, lines 1-15; page 10, lines 24-32 through page 11, lines 1-16 and page 19, line 10 and Figures 4-11 in the specification as originally filed. The foregoing amendments were made without any intention to abandon any subject matter, but with the intention that one or more claims of the same, lesser, or greater scope may be pursued in a later application or in a continuation, continuation-in-part, or divisional application. The present amendment does not add new matter.

The following remarks are responsive to objection/rejections raised by the Examiner in a non-final Office Action, dated September 1, 2006.

Information Disclosure Statement

The Examiner has objected to the information disclosure statement filed on June 21, 2006 as failing to comply with 37 CFR 1.98(a)(2). The Applicants provide herewith a supplemental disclosure statement and PTO/SB/08 form reciting EP294,294 and WO 00/33888 as well as new copies of these foreign references. The Applicants respectfully request consideration of these foreign references.

Claim Rejections -35 U.S.C. § 112, first paragraph—Written Description

The Examiner rejected claim 35 and 38 pursuant to 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Specifically, the Examiner alleges that, the specification as filed does not describe in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner reasons that "the claims encompass a genus of molecules defined solely by its principal biological property, *e.g.*, binds to a polypeptide expressed on a tumor cell, which is simply a wish to know the identity of

the material with that biological property." Office Action, page 5, ¶4. The Applicants traverse the Examiner's rejection of claims 35 and 38 as this rejection is mooted by the cancellation of claims 38 by present amendment and amendment of claim 35 in light of the 37 C.F.R. § 1.132 Declaration by Dr. Mark I. Greene, an expert in the field of Immunology (hereinafter, the "Greene Declaration") which addresses the Examiner's concerns. (See Appendix; EXHIBIT A)

Claim 35 as amended is directed to a method of treating a patient with a tumor comprising drug-resistant tumor cells mediated by p-glycoprotein pump, by administering a compound to the patient which has a formula W-Z-X. The claim recites that X is a chemotherapeutic agent (doxorubicin or paclitaxel); W is a-monoclonal antibody which selectively binds to a polypeptide expressed on the surface of said tumor cells, wherein the polypeptide is selected from the group consisting of p75 neurotrophin receptor (p75), neurotrophic receptor tyrosine kinase (TrKA) and insulin-like growth factor receptor, type 1 (IGF-1R); and Z is a breakable linker which covalently links W and X together, wherein said W, when linked to Z, remains available for binding to the tumor cells, the breakable linker being cleavable in the tumor cells for releasing X into the tumor cells. The release of X into the tumor cells is cytotoxic to the tumor cells, thereby treating the patient.

The analysis of whether the specification complies with the written description requirement is properly based on a comparison of the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. The stated aims of the present invention were to (a) chemically conjugate tumor cell specific binding molecules including specific tumor cell specific monoclonal antibodies to the relatively small chemotherapeutic agent; (b) to afford conjugates that are highly soluble in physiological buffers; (c) chemical coupling should not affect monoclonal antibody targeting function, but should result in inactivation of chemotherapeutic activity; (d) after binding to the target receptor monoclonal antibodies should induce capping and internalization and therefore deliver the conjugate into the tumor cell; (e) the chemical coupling has to allow the release of the chemotherapeutic in its active form after antibody-cytotoxic drug conjugate is internalized. This is achieved by coupling the chemotherapeutic *via* a breakable bond which is cleaved after

conjugate internalization and exposure to lysosomal vesicles. (Specification at page 12, lines 26-32 through page 13, lines 1-6). Consistent with these objectives, the amended claim 35, as a whole, is drawn to a method of treating a patient with a tumor using immunoconjugates as chemotherapeutic agents which can comprise three genus of monoclonal antibodies wherein the immunoconjugate binds to a specified cell surface antigen (*e.g.*, p75 neurotrophin receptor (p75), neurotrophic receptor tyrosine kinase (TrKA) and insulin-like growth factor receptor, type 1 (IGF-1R) polypeptide) and is internalized into the cell to release the chemotherapeutic agent (*i.e.*, doxorubicin or paclitaxel). The Applicants have described such compositions which include monoclonal antibodies directed to p75, TrKA and IGF-1R polypeptide (Specification at page 6, lines 11-13 and claims 1-11 as originally filed) as well as doxorubicin and paclitaxel (a taxane) (Specification at page 5, lines 17-22; page 10, lines 24-33 and page 24, line 16 to 24, line 24; and claims 1-23 as originally filed). The Applicants have demonstrated the utility of such antibodies conjugated to either doxorubicin or paclitaxel compositions as targeted cytotoxic agents in studies utilizing both *in vitro* and *in vivo* models. (See Results Section, Specification at page 21, lines 1-33 through page 26, lines 1-28). The Examiner erroneously asserts that the disclosure of "one species for each genus is insufficient to describe the genus as a whole." (Office Action at page 6, ¶1.).

The Written Description Guidelines detail that a review of compliance with the written description requirement of 35 U.S.C. §112, first paragraph is to be conducted from the standpoint of one of skill in the art at the time the application was filed (*See, e.g.*, Wang Labs. v. Toshiba Corp., 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art. Also, an adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g.*, Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) (the written description "inquiry is a factual one and must be assessed on a case-by-case basis"). Information which is well known in the art need not be described in detail in the specification. *See, e.g.*, Hybritech, Inc. v.

Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). For some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length. MPEP 2163. There is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure. Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also Capon v. Eshhar, 418 F.3d at 1358, 76 USPQ2d at 1084.

The instant application claims the benefit of priority to US provisional patent application USSN 60/256,987, filed December 21, 2000. At the time of the filing of the instant application, the fields of monoclonal antibodies, the techniques for their conjugation as well as site-directed immunotherapy were well-developed arts. (Greene Declaration at ¶4.) Further, receptor-mediated endocytosis was a known biological mechanism for antibody-receptor complexes. (Greene Declaration at ¶4.)

"A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). In the converse, however, it logically follows that the disclosure of a single species can provide support for a genus where the evidence indicates that ordinary artisans can predict the operability in the invention of any species other than the one disclosed.

Although the specification does not disclose the complete structure of multiple species to support each claimed genus of monoclonal antibody-based chemotherapeutic agents, it does disclose the binding characteristics of chemotherapeutic agents comprising monoclonal antibodies (*e.g.*, α-IR3; 5C3; and MC192) directed to p75, TrKA and IGF-1R polypeptide which are three characterized antigens known to be expressed on the surface of tumor cells. In this well-developed art, additional identifying characteristics for a substantial portion of the three genus of chemotherapeutic agents encompassed by amended claim 35 were well-known at the time of filing. As detailed in the Greene's Declaration at ¶ 5, the general knowledge in the art

was that antibodies were structurally well-characterized. A review of the full content of the specification indicates that antibodies such as those that bind to p75, TrKA and IGF-1R polypeptide are essential in the operation of the invention. The level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional. (Greene Declaration at ¶4.) Methodology to conjugate small molecules *via* linkers was known in the art. (Greene Declaration at ¶4.) This is a mature technology where the level of skill is high and advanced. (Greene Declaration at ¶4.)

Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well-defined structural characteristics of antibodies, the functional characteristics of antibody binding, and the fact that the antibody technology is well-developed and mature, one of skill in the art would have recognized that the spectrum of monoclonal antibodies which bind to p75, TrKA and IGF-1R polypeptide were implicitly disclosed in the specification as filed. (Greene Declaration at ¶5.) The disclosure of three individual single species of antibody-based chemotherapeutic agents directed to p75, TrKA and IGF-1R polypeptide on the surface of a tumor cell, including a drug resistant tumor cell provide support for three relevant genus as an ordinary artisan could predict the operability in the invention of any species other than the species disclosed. (Greene Declaration at ¶5.) That is, one of skill in the art would recognize that monoclonal antibody conjugates that recognize the same or other determinants on p75, TrKA, or IGF-1R polypeptide on the surface of the tumor cells would be internalized to affect cytotoxicity. (Greene Declaration at ¶5.) Determination of the classes of monoclonal antibodies-conjugates which bind to p75, TrKA or IGF-1R polypeptide on the surface of a tumor cell, including a drug resistant tumor cell, could be readily determined with a high probability of success by techniques well known in the art at the time the application was filed. (Greene Declaration at ¶5.) As such, the Applicants submit that their disclosure combined with what was known in the art are sufficient to describe the three claimed genus of monoclonal antibody-based chemotherapeutic agents in such full, clear, concise and exact terms to show applicant was in possession of what is now claimed. The Applicants respectfully request

reconsideration and withdrawal of the rejection of the above-referenced claims pursuant to 35 U.S.C. §112, first paragraph for lack of written description.

Claim Rejections -35 U.S.C. § 112, first paragraph—Enablement

The Examiner rejected claims 35 and 39 pursuant to 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. The enablement requirement refers to the requirement of 35 U.S.C. 112, first paragraph that the specification describe how to make and how to use the invention. (MPEP 2164.) It is noteworthy that, in addressing his rejection of claim 35 pursuant to 35 U.S.C. §112, first paragraph for lack of written description, the "Examiner agrees with the Applicant's assertion that one of skill in the art would know how to make and use the invention" from the teachings of the application as originally filed wherein he notes that the written description requirement is severable from the enablement requirement. (Office Action at page 5, ¶3.) The Applicants submit that the Examiner's statement supports the Applicants' assertion that amended claim 35, like claim 35, is enabled by the specification as filed.

The Examiner later alleges that, it is unclear whether a cell line which produces an antibody having the exact chemical identity of α-IR3, 5C3 or MC192 is known or publicly available, or can be reproducibly isolated without undue experimentation. (Office Action at page 6, ¶3). The Examiner states that without a publicly available deposit of the above cell line, one of ordinary skill would not be assured of the ability to practice the invention as claimed. (Office Action at page 6, ¶2). The Applicants traverse the Examiner's rejection as it may apply to claim 35 (now amended) and claim 39 in light of the Greene Declaration which addresses the Examiner's concerns as well as the arguments that follow.

As detailed above, amended claim 35 as a whole, is drawn to a method of treating a patient with a tumor using immunoconjugates as chemotherapeutic agents which can comprise three genus of monoclonal antibodies wherein the immunoconjugate binds to a specified cell surface antigen (*e.g.*, p75, TrkA; and IGF-1R polypeptide) and is internalized into the cell to release the chemotherapeutic agent. Claim 39 is drawn to a method using a monoclonal antibody selected from the group consisting of: α-IR3; 5C3; and MC192.

The Applicants submit that amended claim 35 and claim 39 meet the requirements for enablement of antibody-based compositions and their use. The Federal Circuit's holdings regarding monoclonal antibody compositions differ from other areas of biotechnology such as recombinant DNA. That is, the Court has found monoclonal antibody compositions (In re Wands, 858 F.2d 731, 733-34 (Fed. Cir. 1988), unlike genes or DNA molecules, to be enabled by a specification that describes them by their function without structural description. In Wands, the appellants claimed an immunoassay method for detecting hepatitis-B surface antigen using any IgM monoclonal antibody with a binding affinity constant of greater than 10^9 M. Wands, 858 F.2d at 734-5. The Wands' court found enablement, although the genus of antibodies encompassed by the claim shared a common functional characteristic (*i.e.*, binding hepatitis B surface antigen with high affinity) but wherein the species could be of different amino acid composition. Wands, 858 F.2d at 734. The court focused on enablement, not structure. In re Wands, 858 F.2d at 735-40. The Wands court reasoned that a biological deposit of microorganisms or other living cells is not required to satisfy the enablement requirement where the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine experimentation. Wands, 858 F.2d at 736.

Like Wands, the monoclonal antibodies which bind to p75, TrKA and IGF-1R polypeptide can be made with a high rate of success from readily available starting materials without undue experimentation (*i.e.*, mice; p75, TrKA and IGF-1R polypeptide antigens; and myeloma cells). (Greene Declaration at ¶6.) As detailed above, the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional. (Greene Declaration at ¶4.) This is a mature technology where the level of skill is high and advanced. (Greene Declaration at ¶4.) Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well-defined structural characteristics of antibodies, the functional characteristics of antibody binding, and the fact that the antibody technology is well-developed and mature, one of skill in the art would have recognized that the spectrum of monoclonal antibodies which bind to p75, TrKA and IGF-1R polypeptide were implicitly disclosed in the specification as filed. (Greene Declaration

at ¶5.) The disclosure of three individual single species of antibody-based chemotherapeutic agents directed to p75, TrKA and IGF-1R polypeptide on the surface of a tumor cell, including a drug resistant tumor cell provide support for three relevant genus as an ordinary artisan could predict the operability in the invention of any species other than the species disclosed. (Greene Declaration at ¶5.) That is, one of skill in the art would recognize that monoclonal antibody conjugates that recognize the same or other determinants on p75, TrKA, or IGF-1R polypeptide on the surface of the tumor cells would be internalized to affect cytotoxicity. (Greene Declaration at ¶5.) Determination of the classes of monoclonal antibodies-conjugates which bind to p75, TrKA or IGF-1R polypeptide on the surface of a tumor cell, including a drug resistant tumor cell, could be readily determined with a high probability of success by techniques well known in the art at the time the application was filed. (Greene Declaration at ¶5.) As such, the Applicants believe that amended claim 35 and 39 are in condition for allowance as they are in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph because at the time of filing one of skill in the art would know how to make and use the invention now claimed. The Applicants respectfully request reconsideration and withdrawal of the rejection of the above-referenced claims pursuant to 35 U.S.C. §112, first paragraph for lack of enablement.

Claim Rejections -35 U.S.C. § 102

The Examiner rejected claim 35 pursuant to 35 U.S.C. §102(b) as allegedly anticipated by Trail *et al.* (Clin. Res., 5:3632-38 (1999)) as evidenced by Willner *et al.* (Bioconjugate Chem., 4:521-27 (1993)) and Dietro *et al.* (Braz. J. Med. Biol. Res., 32:925-39 (1999)). The Applicants traverse the rejection of claim 35 under 35 U.S.C. § 102(b) because this rejection is mooted by the present amendment of claim 35. Specifically, the Applicants have amended claim 35 to recite a method of treating a patient with a tumor using immunoconjugates as chemotherapeutic agents which can comprise three genus of monoclonal antibodies wherein the immunoconjugate binds to a specified cell surface antigen (*e.g.*, p75, TrkA; and IGF-1R polypeptide) and is internalized into the cell to release the chemotherapeutic agent.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union

Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Trail *et al.* teaches treating cells which allegedly include paclitaxel-resistant cells with the monoclonal antibody conjugate BDR-96-doxorubicin alone, or in combination with paclitaxel. Trail *et al.* does not teach or suggest the use of an immunoconjugate that binds to the cell surface antigen p75, TrkA, or IGF-1R polypeptide to treat tumor cells, including drug resistant tumor cells. BDR-96 is directed to a Le^y-related tumor-associated antigen. BDR-96-doxorubicin is, therefore, not a monoclonal antibody conjugate directed to p75, TrkA, or IGF-1R polypeptide. Accordingly, Trail *et. al.* does not anticipate amended claim 35. The teachings of Willner *et al.* and/or Dietro *et al.* do not cure the deficiency of Trail *et al.* Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 102(b) rejection of the claim.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance and respectfully request the same. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Dated: March 1, 2007

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